Sulfur ylides
14.* Synthesis of pyrrolo[2,1-*a*]phthalazine-2,6-dione derivative from dioxophthalazine-containing sulfur ylide

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A keto-stabilized sulfur ylide, containing phthalazinedione fragment, was synthesized. During thermolysis, the ylide forms the product of intramolecular cyclization of pyrrolophthalazinedione structure.

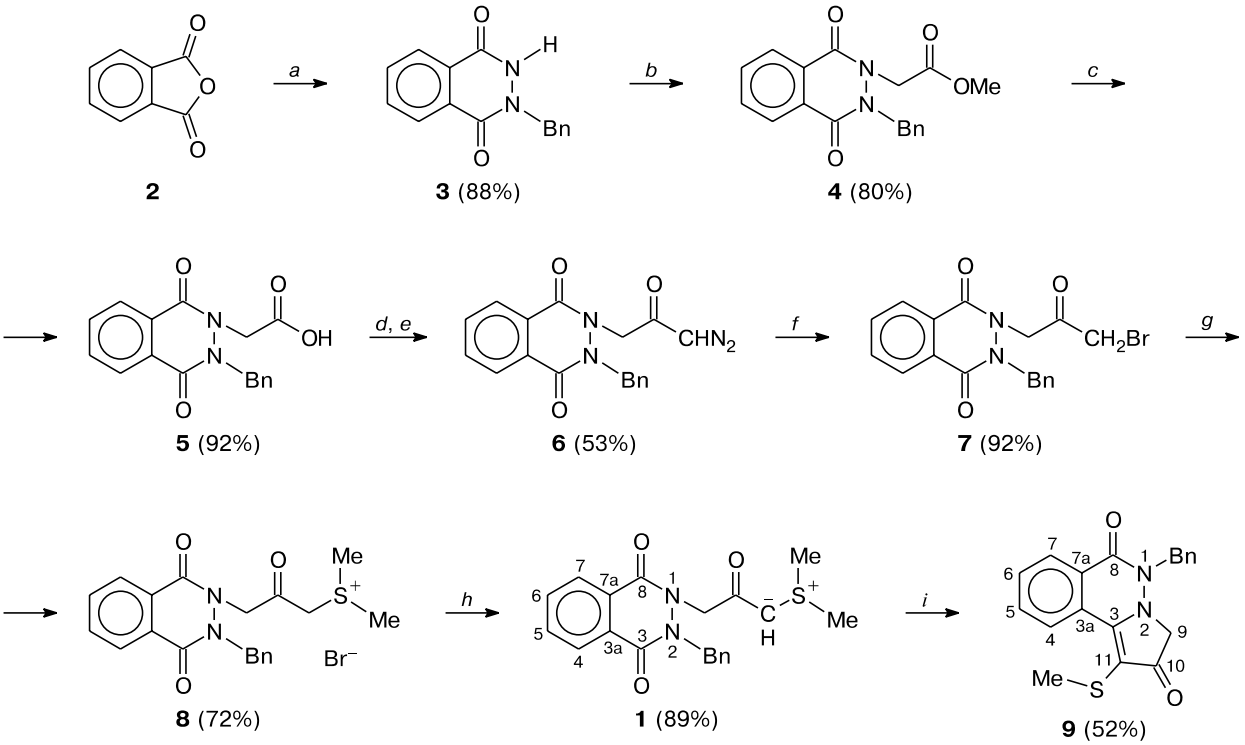
Key words: keto-stabilized sulfonium ylide, intramolecular cyclization, phthalazinedione.

It is known[2,3] that derivatives of 1,4-phthalazinedione, *viz.*, 2-amino- and 5-amino-1,2,3,4-tetrahydro-1,4-phthalazinedione sodium salt (medicine Galavit), show immunomodulating activity.

Earlier,[1,4—6] we discovered a new reaction of intramolecular cyclization of keto-stabilized sulfur ylides, obtained from *N*-phthalyl-protected α- and β-amino acids, which opened a convenient way to the construction of polycyclic compounds with pyrrolizidine- and indolizidinedione structures. The present work is aimed

* For Part 13 see Ref. 1.

Scheme 1



Reagents and conditions: *a*. NH_2NHBn, 140—150 °C; *b*. $BrCH_2COOMe$, $Et_3BnN^+Cl^-$, KOH, THF; *c*. KOH, MeOH; *d*. $SOCl_2$, C_6H_6, reflux; *e*. CH_2N_2, CH_2Cl_2, 5 °C; *f*. HBr, CH_2Cl_2; *g*. Me_2S, CH_2Cl_2; *h*. 12.5 *M* solution of NaOH, K_2CO_3, $CHCl_3$; *i*. BzOH, C_6H_5Me.

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at the synthesis of potentially biologically active compounds with pyrrolophthalazinedione structure with the use of intramolecular cyclization of dioxophthalazine-containing sulfur ylides and at the study of their properties.

The synthesis of dioxophthalazine-containing sulfur ylide **1** was performed starting from the product of the fusion of phthalic anhydride (**2**) with benzylhydrazine in the ratio 1 : 1 (155—160 °C), *i.e.*, from 2-benzyl-2,3-dihydrophthalazine-1,4-dione (**3**) (Scheme 1). Alkylation of the latter with methyl bromoacetate under the phase transfer catalysis conditions and ultrasonic treatment led to methyl 3-benzyl-1,4-dioxo-1,2,3,4-tetrahydrophthalazin-2-ylacetate (**4**). The alkaline hydrolysis of compound **4** in methanol gave rise to 3-benzyl-1,4-dioxo-1,2,3,4-tetrahydrophthalazin-2-ylacetic acid (**5**), which upon treatment with thionyl chloride was transformed to the acyl chloride. The latter without isolation was converted to diazoketone **6** upon treatment with a solution of CH_2N_2 in CH_2Cl_2.

The reaction of compound **6** with aqueous HBr gives bromoketone **7**, which upon treatment with Me_2S forms sulfonium salt **8**. The deprotonation of salt **8** with a mixture of saturated aq. potash and 12.5 *M* aq. sodium hydroxide leads to sulfur ylide **1**.

The reflux of sulfur ylide **1** in toluene in the presence of equimolar amount of benzoic acid gives the product of intramolecular cyclization **9** in 52% yield. The structure of pyrrolophthalazinedione **9** obtained was confirmed by spectral methods: in the ^{1}H NMR spectrum, a singlet of three protons of the methylthio group at δ 2.41 is observed, in the ^{13}C NMR spectrum, C(11) and C(3) atoms of the double bond resonate at δ 123.6 and 147.0, respectively. It should be noted that methyl benzoate was also formed during the reaction, which was identified by GLC.

In conclusion, a method for the synthesis of pyrrolo[2,1-*a*]phthalazine-2,6-dione derivative on the basis of 2-benzyl-2,3-dihydrophthalazine-1,4-dione was elaborated.

Experimental

IR spectra were recorded on a UR-20 and Specord M-80 spectrometers for suspensions in Nujol. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-AM-300 (300 and 75 MHz, respectively) for solutions in $CDCl_3$, Me_4Si was used as the internal standard. The reaction course was monitored by TLC on Silufol UV-254 plates with visualization of substances in the UV light, iodine vapors, and by spraying of the plates with ninhydrin spray reagent or with anisaldehyde solution with subsequent heating at 100—120 °C. Acetone, CH_2Cl_2, and ethyl acetate were distilled over P_2O_5. Toluene, THF, and light petroleum were refluxed and distilled over sodium metal; Me_2S was dried over molecular sieves 4A. Pure for analysis HBr was used as 48% aq. solution; thionyl chloride (pure for analysis) and benzoic acid (pure) were used without additional purification. Reaction products **4** and **6** were isolated by column chromatography on silica gel (eluent: light petroleum—ethyl acetate, 8 : 2).

2-Benzyl-2,3-dihydrophthalazine-1,4-dione (3). A mixture of finely ground phthalic anhydride (**2**) (4 g, 27 mmol) and benzylhydrazine (3.30 g, 27 mmol) was heated for 15 min on an oil bath at 155—160 °C. After cooling, the solid reaction product was dissolved in hot methanol (20 mL), the solution was filtered and diluted with water (20 mL). The precipitate formed was filtered off and washed with ether. The yield was 5.98 g (88%), m.p. 197—199 °C. Found (%): C, 71.47; H, 4.73; N, 11.13. $C_{15}H_{12}N_2O_2$. Calculated (%): C, 71.42; H, 4.79; N, 11.10. ^{1}H NMR ($CDCl_3$), δ: 1.26 (s, 1 H, NH); 5.28 (s, 2 H, CH_2); 7.27—7.47 (m, 5 H, Ph); 7.83—8.47 (m, 4 H, C_6H_4).

Methyl 3-benzyl-1,4-dioxo-1,2,3,4-tetrahydrophthalazin-2-ylacetate (4). A mixture of phthalazinedione **3** (1 g, 3.96 mmol), methyl bromoacetate (1.2 g, 7.92 mmol), ground KOH (0.22 g, 3.96 mmol), and triethylbenzylammonium chloride (14 mg, 0.06 mmol) in THF (10 mL) was subjected to ultrasound treatment (UZDN-2T, operating frequency, 22 kHz) for 40 min. The reaction mixture was filtered off from the precipitate, the solvent was evaporated. The target product was isolated by column chromatography. The yield was 1.03 g (80%), m.p. 93—95 °C. Found (%): C, 66.69; H, 4.87; N, 8.61. $C_{18}H_{16}N_2O_4$. Calculated (%): C, 66.66; H, 4.97; N, 8.64. IR, ν/cm^{-1}: 1620, 1650, 1760. ^{1}H NMR ($CDCl_3$), δ: 3.91 (s, 3 H, Me); 4.81, 5.18 (both s, 2 H each, CH_2); 7.19—7.37 (m, 5 H, Ph); 7.71—8.39 (m, 4 H, C_6H_4).

3-Benzyl-1,4-dioxo-1,2,3,4-tetrahydrophthalazin-2-ylacetic acid (5). A solution of potassium hydroxide (0.84 g, 15 mmol) in minimum water was added in one portion to a stirred suspension of ester **4** (1 g, 3 mmol) in methanol (20 mL) at ~20 °C. A practically instant dissolution of the ester took place, after this, the solution was stirred for another 20 min, the solvent was evaporated, then water (10 mL) was added and the mixture was extracted with ethyl acetate until the color in the organic layer disappeared. The aqueous layer was acidified with hydrochloric acid to pH 1—2, the precipitate of white color that formed was filtered off and dried in air. The yield was 0.88 g (92%), m.p. 152—155 °C. Found (%): C, 65.83; H, 4.51; N, 9.09. $C_{17}H_{14}N_2O_4$. Calculated (%): C, 65.80; H, 4.55; N, 9.03. IR, ν/cm^{-1}: 1580, 1740, 3140.

3-Benzyl-2-(3-diazo-2-oxopropyl)-2,3-dihydrophthalazine-1,4-dione (6). Thionyl chloride (1.82 mL, 25.14 mmol) was added to a suspension of acid **5** (2.6 g, 8.38 mmol) in anhydrous benzene (15 mL) and this was refluxed until evolution of a gas ceased (~6 h). After evaporation of the solvent and excess of thionyl chloride, the acyl chloride obtained was used without additional purification. A solution of the acyl chloride (2.67 g, 8.12 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred and cooled to −5 °C solution of diazomethane, obtained from nitrosomethylurea (3.35 g, 40.6 mmol). The solvent was evaporated the target product was isolated by column chromatography. The yield was 1.5 g (53%), m.p. 79—81 °C. Found (%): C, 64.68; H, 4.25; N, 16.73. $C_{18}H_{14}N_4O_3$. Calculated (%): C, 64.66; H, 4.22; N, 16.76. IR, ν/cm^{-1}: 1592, 1663, 2120. ^{1}H NMR ($CDCl_3$), δ: 4.82 (s, 2 H, CH_2); 5.28—5.31 (m, 2 H, CH_2); 5.56 (s, 1 H, CH); 7.17—7.49 (m, 5 H, Ph); 7.73—8.48 (m, 4 H, C_6H_4).

3-Benzyl-2-(3-bromo-2-oxopropyl)-2,3-dihydrophthalazine-1,4-dione (7). A concentrated aq. solution of HBr (2.75 mL) was added dropwise to a stirred solution of diazoketone **6** (1.1 g,

3.3 mmol) in CH_2Cl_2 (10 mL), after this, the mixture was refluxed for 1 h, cooled, and diluted with three-fold volume of water. The organic layer was separated, washed with soda solution, and dried with magnesium sulfate. The solvent was evaporated, bromoketone obtained was recrystallized from ether. The yield was 1.16 g (92%), m.p. 135—136 °C. Found (%): C, 55.85; H, 3.88; Br, 20.68; N, 7.27. $C_{18}H_{15}BrN_2O_3$. Calculated (%): C, 55.83; H, 3.90; Br, 20.63; N, 7.23. IR, ν/cm^{-1}: 1659, 1762. ^{1}H NMR ($CDCl_3$), δ: 3.84, 5.07, 5.25 (all s, 2 H each, CH_2); 7.23—7.45 (m, 5 H, Ph); 7.78—8.47 (m, 4 H, C_6H_4).

[3-(3-Benzyl-1,4-dioxo-2,3-dihydrophthalazin-2-yl)-2-oxopropyl]dimethylsulfonium bromide (8). A solution of bromoketone **7** (1 g, 2.58 mmol) and dimethyl sulfide (9.2 mL, 7.74 mmol) in CH_2Cl_2 (10 mL) was stirred for 5 h. The reaction mixture was kept for ~14 h at ~20 °C. The precipitate formed was filtered and washed with CH_2Cl_2. The yield was 0.83 g (72%), m.p. 126—127 °C. Found (%): C, 53.49; H, 4.69; Br, 17.75; N, 6.27; S, 7.11. $C_{20}H_{21}BrN_2O_3S$. Calculated (%): C, 53.46; H, 4.71; Br, 17.78; N, 6.23; S, 7.14. IR, ν/cm^{-1}: 1455, 1478, 1674.

[3-(3-Benzyl-1,4-dioxo-2,3-dihydrophthalazin-2-yl)-2-oxopropylidene]dimethylsulfuran (1). A mixture of sodium hydroxide (0.15 mL of 12.5 *M* solution) and saturated aq. potash (0.8 mL) was added in one portion to a stirred (10 °C) suspension of sulfonium salt **8** (600 mg, 1.33 mmol) in chloroform (15 mL). The reaction mixture was stirred for 15 min, after the temperature reached ~20 °C, the precipitate was filtered off. The layers were separated, the organic layer was dried with K_2CO_3, the solvent was evaporated to obtain a crystalline product of dark orange color. The yield was 439 mg (89%), m.p. 43—44 °C. Found (%): C, 65.23; H, 5.45; N, 7.57; S, 8.72. $C_{20}H_{20}N_2O_3S$. Calculated (%): C, 65.20; H, 5.47; N, 7.60; S, 8.70. IR, ν/cm^{-1}: 1540, 1590, 1650. ^{1}H NMR ($CDCl_3$), δ: 2.81 (s, 6 H, 2 Me); 3.96 (s, 1 H, CH); 4.68, 5.16—5.28 (both m, 2 H each, CH_2); 7.13—7.49 (m, 5 H, Ph); 7.66—8.37 (m, 4 H, C_6H_4). ^{13}C NMR, δ: 28.4 (2 Me); 51.1 (CH); 53.9 ($\underline{C}H_2Ph$); 69.2 (CH_2); 123.2, 127.4, 127.0 (CH_{Ph}); 124.5 (C(3a)), 129.0 (C(7a)); 137.0 ($CH_2\underline{C}_{Ph}$); 128.2 (C(7)); 128.7 (C(4)); 131.6 (C(5)); 132.5 (C(6)); 145.0 (C(3)); 158.2 (C(8)); 184.0 (C=O).

5-Benzyl-1-(methylthio)pyrrolo[2,1-*a*]phthalazine-2,6(3*H*,5*H*)-dione (9). Benzoic acid (139 mg, 1.14 mmol) was added to a solution of sulfur ylide **1** (420 mg, 1.14 mmol) in anhydrous toluene (10 mL). The reaction mixture was refluxed for 30 min. Toluene was evaporated, the product was isolated by column chromatography on SiO_2 (eluent: ethyl acetate—hexane, 1 : 3). The yield was 200 mg (52%), m.p. 142—146 °C. Found (%): C, 67.87; H, 4.82; N, 8.31; S, 9.55. $C_{19}H_{16}N_2O_2S$. Calculated (%): C, 67.84; H, 4.79; N, 8.33l; S, 9.53. IR, ν/cm^{-1}: 1327, 1637, 1691. ^{1}H NMR ($CDCl_3$), δ: 2.41 (s, 3 H, Me); 5.01—5.03, 5.14—5.28 (both m, 2 H each, CH_2): 6.94—7.50 (m, 5 H, Ph); 7.77—8.46 (m, 4 H, C_6H_4). ^{13}C NMR, δ: 25.7 (MeS); 54.0 (C(9)); 69.1 ($\underline{C}H_2Ph$); 123.2 (C(5)); 123.6 (C(11)); 127.5 (C(7)); 127.6, 128.4, 128.6 (CH_{Ph}); 129.3 (C(7a)); 129.8 (C(6)); 130.1 (C(4)); 136.8 ($CH_2\underline{C}_{Ph}$); 147.0 (C(3)); 158.4 (C(3a)); 164.5 (C(8); 199.0 (C(10)).

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